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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,748	10/06/2006	Joseph R. Garlich	050990.0201.02USPC	3652
27148 7590 04/29/2009 POL SINELLI SHUGHART PC 700 W. 47TH STREET SUITE 1000 KANSAS CITY, MO 64112-1802				
EXAMINER				
RAE, CHARLESWORTH E				
ART UNIT		PAPER NUMBER		
1611				
MAIL DATE		DELIVERY MODE		
04/29/2009		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/599,748

**Applicant(s)**

GARLICH ET AL.

**Examiner**

CHARLESWORTH RAE

**Art Unit**

1611

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 30 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) 1-4 and 7-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 5-6, and 13-14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/S5108)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114. By Amendment filed October 17, 2005, claims 8-12, 19, 28, 34, 46, 47, 50 and 55-58 have been amended. Claims 8-12, 19-28, 34-36, 46-51, 55-58 and 67-74 are currently pending for prosecution on the merits.

#### **Status of the Claims**

Claims 1-14 are currently pending in this application.

Claims 1-4, and 7-12, are withdrawn for being directed to non-elected subject matter.

Claims 5-6 and 13-14 are under examination.

#### **Claim Amendment**

Claim amendment, received 01/30/09, is acknowledged and made of record.

#### **Allowable Subject Matter**

The previous indication of allowable subject matter regarding the compound recited in instant claim 13 is withdrawn in view of the new rejection set forth below.

#### **Response to applicant's arguments**

##### **Rejection under 102(b)**

This rejection is withdrawn in view of the claim amendment.

### **REJECTION**

### **Claim rejections – 35 USC 103(a)**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

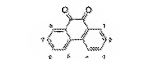
**Claims 5-6 and 13-14 are rejected under 103(a) as being unpatentable over Urbanek et al. (Urbanek et al. Potent reversible inhibitors of the protein tyrosine phosphatases CD45. Journal of Medicinal Chemistry. 2001; 44(11):1777-1793), in view of Mandrusov et al. (US Patent 7,008,411).**

Urbanek et al. (Urbanek et al. Potent reversible inhibitors of the protein tyrosine phosphatases CD45. Journal of Medicinal Chemistry. 2001; 44(11):1777-1793).

Urbanek et al. teach 9,10-phenanthrenedione CD45 selective inhibitor compounds having potent inhibitory effects on T-cell receptor mediate proliferation, wherein said compounds have the below general formula, wherein no more than one of

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R1, R2, R3, and R4 is hydrogen (page 1777, col. 1, second full para. to col. 2, 4th line, including figures 2-3; page 1783, Table 2; and pages 1784-1785, Table 3):



Urbanek et al. state that CD45 is a family of transmembrane protein tyrosine phosphatases (PTPs) that are expressed exclusively by hemopoietic cells and that CD45 plays a critical role in T-cell receptor (TCR)-mediated signaling by regulating the phosphorylation and activity of src-family protein tyrosine kinases and their substrates (page 1777, col. 2, last para.).

In particular, Urbanek teach the below compound species (pages 1784-1785, Table 3):

4	NO <sub>2</sub>	2	2.4 ± 0.2	1.6 ± 0.4	10.0 ± 2.0
52	NO <sub>2</sub>	3	0.5 ± 0.1	0.2 ± 0.0	2.8 ± 0.6
5	NO <sub>2</sub>	4	0.5 ± 0.0	1.3 ± 0.2	10.0 ± 1.5
53	NO <sub>2</sub>	2, 7	4.1 ± 0.6	0.5 ± 0.01	8.0 ± 2.5
54	NO <sub>2</sub>	2, 5	>30	>30	>30
2	Br	2	0.4 ± 0.2	0.6 ± 0.5	5.0 ± 1.7
55	CO <sub>2</sub> H	2	1.0 ± 0.2	>30	>30

68		2	0.5 ± 0.3	1.0 ± 0.4	14.0 ± 2.5
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In addition, Urbanek et al. teach the below compounds (page 1783, Table 2):

compd	R1	R2	R3	R4	pNPP IC <sub>50</sub> , μM	4-k IC <sub>50</sub> , μM	protif. IC <sub>50</sub> , μM	GC <sub>50</sub> , μM
47	NH <sub>2</sub>	H	H	H	>30	>30	7.8 ± 0.8	9.0 ± 0.6
3	H	NH <sub>2</sub>	H	H	0.4 ± 0.1	2.3 ± 0.9	0.2 ± 0.0	5.0 ± 1.0
48	H	H	NH <sub>2</sub>	H	3.7 ± 1.5	10.5 ± 2.2	0.2 ± 0.1	17.0 ± 3.5
49	H	H	H	NH <sub>2</sub>	0.8 ± 0.2	2.9 ± 1.5	0.2 ± 0.1	9.0 ± 2.0
50	NHCH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	H	H	H	0.4 ± 0.1	4.7 ± 1.2	0.5 ± 0.2	9.0 ± 2.3
51	H	H	NHCH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	H	0.4 ± 0.1	3.2 ± 0.7	1.0 ± 0.3	18.0 ± 2.5

\* The reported values are the mean of all experiments, and the errors are standard errors of the mean.

Urbanek et al. disclose that CD45 plays a critical role in T-cell receptor (TCR)-mediated signaling by regulating the phosphorylation and activity of scr-family protein tyrosine kinases and their substrates (page 1777, col. 2, last para.). Urbanek et al. state that current therapies targeted at reducing immune-cell activation in conditions associated with inappropriate lymphocyte and monocyte/macrophage activation, such as organ transplant rejection and autoimmune diseases (such as multiple sclerosis and rheumatoid arthritis) also affect cells outside of the immune system and consequently carry the liability of toxic side effects (page 1777; col. 1, lines 1-8). Urbanek state that immunosuppressants such as cyclosporine and FK506, which inhibit IL-1 production in T-cells by blocking the phosphatase activity of calcineurin, can also cause renal toxicity, neurotoxicity, and the increased risk of malignancy (page 1777, col. 1, lines 8-12), while the antiproliferative effects of rapamycin, which inhibits T-cell proliferation further down the signaling pathway by inhibiting the autocrine response of T-cells to IL-2 by binding to and blocking a kinase essential for cell cycle progression, are not limited to cells of the immune system and can affect growth factor-induced proliferation of fibroblasts, endothelial cells, hepatocytes, and smooth muscle cells (page 1777, col. 1, lines 12-29).

However, Urbanek et al. do not teach the instant claimed method for treating damage to normal tissue attributable to heart disease, or the specific instantly claimed compound recited in claim 13 (i.e. reference compound 68 has an extra CH<sub>2</sub> linker attaching the O atom to the phenyl ring; the O atom is directly attached to the phenyl of the instant claimed compound).

Mandrusov et al. (US Patent 7,008,411) teach a method for treating coronary artery and related diseases, including, for example, atherosclerotic occlusions and vulnerable plaque (col. 3, lines 45-59). Mandrusov et al. teach that a drug eluting stent may be implanted at the region of the vessel occlusion to treat the occlusive atherosclerosis (i.e. non-vulnerable plaque) while releasing a drug or biologically active agent to treat said atherosclerosis (i.e. non-vulnerable plaque). See col. 4, lines 27-36). Manrusov et al. state that plaque stabilization could be achieved through inhibition of extracellular matrix degradation by preventing the accumulation of macrophages and T lymphocytes in the vulnerable plaque or by inhibiting the proteolytic enzyme cascade directly (col. 7, line 64 to col. 8, lines 1). Mandrusov state that examples of therapeutic or biologically active agents include, but are not limited to, rapamycin, ..., antiproliferative substances, antineoplastic agents, ..., alpha-interferon, ..., and dexamethasone (col. 12, line 64 to col. 13, line 15). Mandrusov et al. teach that the biologically active agent may be loaded onto a stent in a dose of 10-600 µg, or 300 micrograms of an angiogenic agent (col. 9, lines 39-49; and col. 13, lines 15-16).

It would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references to treat a patient with coronary heart disease as taught by Mandrusov et al. with a CD45 selective inhibitory compound of Urbanbek et al. (e.g. compound 49, wherein R1 is hydrogen; or compound 68, wherein R1 is  $\text{NHCOCH}_2\text{OPh}$ ; (abstract; page 1783 Table 2, compound 49; and 1785, Table 3, compound 68) to control atherosclerotic occlusions and vulnerable plaque (col. 3, lines 45-59). One would have been motivated to do so because

Mandrusov suggest that therapeutic or biologically active agents including rapamycin and antiproliferative substances may be used to treat coronary artery and related diseases, including, for example, atherosclerotic occlusions and vulnerable plaque (col. 3, lines 45-59; and col. 12, line 64 to col. 13, line 15) and Urbanek et al. teach 9,10-phenanthrenedione compounds that possess antiproliferative activity, wherein said antiproliferative activity is selective for CD45 (page 1777, col. 2, last para.). Also, Urbanek et al. suggest that 9,10-phenanthrenedione CD45 inhibitors are more selective antiproliferative agents than current antiproliferative agents, for example, rapamycin (page 1777, col. 1, lines 12-29) and that current therapies targeted at reducing immune-cell activation in conditions associated with inappropriate lymphocyte and monocyte/macrophage activation carry the liability of toxic side effects (page 1777; col. 1, lines 1-8).

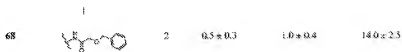
Further, it would have been obvious to a person of skill in the art at the time the invention was made to attempt to manipulate the R1 substituent by altering the chain length of the benzyloxy moiety (i.e. substituting a benzyloxy with a phenoxy group) to arrive at the instant claimed compound to optimize the therapeutic profile of the compound in view of the homology between the reference compound and the instant compound as evidenced by the above structures. One would have been motivated to do so since homologs are prima facie obvious because one of skill in the art would expect that compounds similar in structure will have similar properties (MPEP 2144.08-2144-09; see also *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979) and Urbanek et al. teach compounds, wherein modification of the chain length of the R1

substituent does not appear to significantly alter the therapeutic utility of said compounds (page 1784-1785, Table 3).

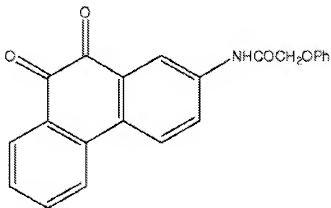
Regarding claim 5, Urbanek et al. teach compound 49, wherein R1 is hydrogen, which reads on the general formula recited in claim 5 (page 1783, Table 2). Since Urbanek et al. teach compounds that read of the general formula recited in claim 5, one would reasonably expect that said compounds taught by Urbanek et al. would exhibit the same therapeutic effects as claimed, including inhibiting PTEN. Further, one would reasonably expect to rely on the teaching of the dose amount of therapeutically active agents as taught by Mandrusov et al. to treat a patient with coronary heart disease by administering a compound of Urbanek et al. in a dose amount of 10-600 µg, which is considered to be "pharmaceutically acceptable amount (col. 9, lines 39-49; and col. 13, lines 15-16).

Regarding claim 6, Mandrusov et al. teach that a drug eluting stent may be implanted at the region of the vessel occlusion to treat the occlusive atherosclerosis (i.e. non-vulnerable plaque) while releasing a drug or biologically active agent to treat said atherosclerosis (i.e. non-vulnerable plaque; col. 4, lines 27-36) such that one would reasonably expect to successfully administer a compound of Urbanek et al. with a stent to treat a patient with occlusive atherosclerosis and it is well known that stents serve as a treatment for occlusive atherosclerosis as well.

Regarding claim 13, Urbanek et al. teach that below compound (page 1785, Table 3):



The only difference between the above reference compound 68 and applicant's below compound as recited in claim 13, is that the above reference compound 68 has an extra CH<sub>2</sub> linker separating the O atom from the phenyl ring:



In view of the homology between the reference compound and the instant claimed compound, one would reasonably expect to attempt to modify the reference compound to arrive at the instant claimed compound since compounds with similar structures, wherein the only difference between the structures is a CH<sub>2</sub> linker group, would reasonably be expected to have similar utilities absent objective evidence to the contrary.

Regarding the term "wherein the PTEN inhibitor is administered prior to, together with, or after a treatment for a disease suffered by the patient," the above discussion of claim 6 is incorporated by reference.

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

#### **Response to applicant's arguments**

Applicant's arguments with respect to the rejection under 103(a) have been considered but are moot in view of the new ground(s) of rejection.

#### **Relevant Art of Record**

The below cited art made of record and relied upon is considered pertinent to applicant's invention and is cited to show the general state of the art regarding the therapeutic utility of PTEN inhibitors.

Durden (US Patent 6,777,439) teaches PTEN inhibitors and methods of using said compounds for treating aberrant angiogenesis associated with several diseases, including cancer, autoimmune diseases, coronary artery diseases, and atherosclerosis (col. 2, lines 44-54).

#### **Conclusion**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

18 April 2009  
/C. R./ Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611